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Intestinal failure as a significant risk factor for renal impairment in children

Running head: Renal function of children with intestinal failure

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Authors' contribution

EY, LM-S, MP and TJ designed the study. EY wrote the manuscript draft, EY, RG, LM-S and MP collected the data. EY performed statistical analysis. EY, LM-S, RG, MP and TJ took part in the discussion of the results, revised the paper and agreed with the final version of the paper.

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Abstract

Objective: While impaired renal function has been a frequent finding among adult patients with intestinal failure (IF), the data on children is scarce. This study aimed to assess renal function in pediatric-onset IF.

Methods: Medical records of 70 patients (38 boys) with pediatric onset IF due to either short bowel syndrome (SBS, n=59) or primary motility disorder (n=11) and a history of parenteral nutrition (PN) dependency for at least one month were evaluated. Renal function at the most recent follow-up was studied using plasma creatinine, cystatin C and urea concentrations and estimated glomerular filtration rate (eGFR).

Results: At a median age of 5.7 and after PN duration of 3.2 years, twenty (29%) patients had decreased eGFR and higher cystatin C and urea concentrations. Patients with decreased renal function had significantly longer duration of PN (3.2 years versus 0.9 years, p=0.030) and shorter percentage of age-adjusted small bowel length remaining (22% versus 32%, p=0.041) when compared to patients with preserved renal function. No other predisposing factors for decreased eGFR were identified.

Conclusions: Patients with pediatric onset IF are at significant risk of impaired renal function, which associated with the severity of SBS. Further studies using measured GFR are needed.

Key Words: intestinal failure; short bowel syndrome; pediatric; parenteral nutrition; kidney

Background

The European Society of Clinical Nutrition and Metabolism has defined intestinal failure (IF) as the reduction of gut function below the minimum necessary for the absorption of macronutrients, water and electrolytes, so that intravenous supplementation is required to maintain health and growth [1]. In pediatric patients, necrotizing enterocolitis, intestinal atresia, mid-gut volvulus, gastroschisis, Hirschsprung disease and intestinal pseudo-obstruction (CIPO) causing either short bowel syndrome (SBS) or severe intestinal dysmotility are the most common etiologies for IF [2,3].

Patients with IF are at persistent risk of hypovolemia and electrolyte imbalance due to impaired absorption and increased intestinal losses, recurrent sepsis episodes and nephrotoxic medications, which may have an adverse effect on kidney function. Impaired kidney function and development of chronic renal failure have been reported in adult patients with long-term parenteral nutrition for IF [4-7] whereas data on renal function in children with IF is very limited [8,9]. Chronic renal failure is observed earlier and more frequently following intestinal transplantation when compared to other solid organ transplantations [10]. The golden standard for evaluating renal function is to measure the glomerular filtration rate (mGFR) using either inulin or some other radio-labeled marker, such as ethylenediamine tetracetic acid labeled chromium-51 (^{51}Cr-EDTA). Due to the costs and complexities of measuring GFR, estimated GFR, plasma creatinine and cystatin C are often used in clinical practice to assess renal function. Renal function is considered to be impaired if GFR is < 90mL/min/1.73m^2 in adults and children older than two years of age [11]. The aim of the present study was to assess the renal function in children with IF during and after weaning off PN.

Materials and methods

The study comprised patients with pediatric onset IF treated and followed up at the Children's Hospital, Helsinki University Hospital, between the years 1990 and 2015. All patients with IF due to either SBS or primary intestinal dysmotility disorders and with parenteral nutrition (PN) for at least for one month and a follow-up period of at least one year were included. In total, 78 eligible patients were identified; eight of them were excluded from the study because of incomplete laboratory values.

Patient's age, sex, primary disease, cause of IF, surgical procedures, number of blood culture positive sepsis episodes, anatomy of the remaining bowel, duration of PN, and the amount of current PN as well as weight and height at the most recent follow-up were collected from the patient records. Sepsis episode details could be reliably extracted from the electronic hospital discharge database from the year 1993 onwards. Six out of the 70 patients were born before 1993, and data on their early sepsis episodes may therefore not be complete.

Growth was assessed using the Finnish national growth charts. The height is given as z scores and weight as age-adjusted ISO-BMI scores for patients ≥ 2 years. Height was corrected for gestational age if needed. Age-adjusted weight-to-height percentiles (based on the national data) are reported for those < 2 years [12]. Three patients with cartilage-hair hypoplasia and one patient with Down syndrome-associated growth failure were excluded from the height analysis. The percentage of the remaining age-adjusted small bowel and colon length was calculated based on age-specific normal *in vivo* values [13]. Hirschsprung disease patients with less than 50% of age-adjusted small bowel length remaining were categorized to the SBS group.

Renal function laboratory parameters (plasma creatinine, cystatin C and urea) measured at the time of the most recent follow-up visit were collected from the medical records; the follow-up time was considered to end at this point. Renal function was evaluated using either the estimated

glomerular filtration rate (eGFR) calculated by the CKID Schwartz equation [14], which uses all creatinine, cystatin C and urea values in the formula or the CKD-EPI Creatinine-Cystatin equation [15] for patients older than 18 years of age. In two cases lacking cystatin C value, creatinine-based Bedside Schwartz formula was used [16]. In four cases with decreased renal function, GFR had been evaluated more precisely using ^{51}Cr-EDTA measurement. Renal function was classified as normal when eGFR was ≥ 89 mL/min/1.73m^2 (≥ 62 mL/min/1.73m^2 at the age of 12 to 19 months) [17]. In patients who underwent intestinal transplantation during follow-up, renal function was evaluated before the surgery. Renal ultrasound had been performed on all patients with decreased renal function. The possible presence of structural abnormalities, nephrocalcinosis and/or increased echogenicity was recorded from the medical records and ultrasound pictures.

Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS/Windows version 22.0, SPSS Inc., Chicago, IL, USA). Data are reported as medians with their interquartile range. A Mann-Whitney U test was used to compare median values. Fisher's exact test was used for comparison of categorical variables. Statistical significance was defined as $P \leq 0.05$.

Ethics

The Ethical Committee of the Children's Hospital, University of Helsinki, approved the use of patient's information and the study protocol.

Results

The demographics and clinical characteristics of the patient population are summarized in **Table 1**. The causes of IF included necrotizing enterocolitis (n=20), mid-gut volvulus (n=15),

small bowel atresia (n=14), gastroschisis (n=2), CIPO (n=8), and Hirschsprung's disease (n=11); eight of these were categorized to the SBS group. At the latest follow-up visit, 22 of the 70 (31%) patients were on PN and received a median 7 (6-7) weekly PN infusions. Five patients have undergone intestinal transplantation and three are currently on waiting list for transplantation.

Table 1. Patient characteristics of 70 patients with pediatric onset IF having either normal or decreased GFR at the end of the follow-up.

	All patients	Patients with decreased GFR*	Patients with normal GFR*	P-value
N	70	20	50	
Boys	38	10	28	0.792
Age/Follow-up time (yrs)	5.4 (3.3-12.3)	5.7 (3.0-12.1)	5.4 (3.6-14.2)	0.563
Height (z score)	-1.4 (-2.3 to -0.4)	-2.5 (-3.2 to -0.7)	-1.1 (-2.0 to -0.1)	**0.027**
Weight (ISO-BMI)	19.6 (17.3-22.0)	20 (18.9-22.4)	19.2 (16.4-21.9)	0.207
Weight (percentiles)	-9% (-11 to -0)	0	-9 % (-11 to-2)	0.667
SBS/Dysmotility disorder	59/11	19/1	40/10	0.159
Patients weaned off PN	48	12	36	0.397
Time after weaning off PN (yrs)	4.5 (2.2-9.7)	4.0 (1.7-7.1)	4.9 (2.3-10.7)	0.338
Duration of PN (months)	14.7 (6.3-40.0)	38.7 (11.5-99.2)	11.1 (5.2-32.0)	**0.030**
Amount of curr. PN (kcal/kg/day)	41.5 (30.7-60)	50.5 (35.3-74.7)	38.4 (30.0-45.0)	0.297
N of septicemia/patient	1.0 (0.0-2.0)	0.0 (0.0-3.5)	1.0 (0.0-2.0)	0.863
Remaining bowel				
Small bowel (cm)	50 (30-100)	36 (23-65)	50 (31-103)	0.364

Small bowel (%)	26 (17-53)	22 (16-32)	32 (21-75)	**0.041**
Colon (%)	77 (50-100)	72 (3-100)	82 (50-100)	0.462
Colon +/-	45/15	14/6	41/9	0.337
ICV preserved	34	7	26	0.290
Plasma creatinine µmol/L	33 (24-48)	43 (28-53)	30 (22-46)	0.062
Plasma cystatin C mg/L	0.85 (0.74-0.98)	0.99 (0.90-1.18)	0.76 (0.72-0.86)	**<0.001**
Plasma urea mmol/L	4.9 (3.9-6.6)	6.8 (4.8-7.2)	4.5 (3.7-5.2)	**<0.01**
eGFR mL/min/1.73m^2	100 (86-115)	71 (65-86)	107 (99-124)	**<0.001**

Curr. = current, eGFR = estimated glomerular filtration rate, ICV = ileocecal valve, ISO-BMI = age-adjusted BMI, N = number, SBS = short bowel syndrome, PN = parenteral nutrition, yrs = years. *Renal function was classified as normal when eGFR was ≥ 89ml/min/1.72m^2 (≥ 62 mL/min/1.73m^2 at the age of 12 to 19 months) [17].

Overall, 20 (29%) patients had decreased eGFR at a median age of 5.7 years after median PN duration of 3.2 years (**Table 1**). Patients with decreased eGFR had also significantly higher cystatin C and urea values. The increase in creatinine levels failed to reach statistical significance. Among patients with decreased renal function, eGFR was 60-89 mL/min/1.73m^2 in 16 (80%) patients and below 60mL/min/1.73m^2 in four (20%) patients. There was no difference between patients treated in 1990–2000 to those treated in 2000–2015, the mean GFR being 108 versus 97 mL/min/1.73m^2 (p=0.395).

The duration of PN was significantly longer among patients with decreased eGFR when compared to patients with normal renal function (**Table 1**). The duration of PN remained significantly longer among patients with decreased eGFR also after patients with CIPO or Hirschprung disease with more than 50% of age-adjusted small bowel length remaining were excluded from the analysis (p=0.020). The percentage of age-adjusted length of the remaining

small bowel was also significantly lower in patients with decreased renal function than in patients with normal GFR (**Table 1**). Patients with decreased renal function were also shorter than patients with normal renal function (**Table 1**). There was no association between the cause of IF, current PN delivery, the follow-up time after weaning off PN, the number of blood culture-positive sepsis episodes, weight, the absolute length of remaining small bowel, remaining colon or the presence of ileocecal valve and decreased eGFR (**Table 1**). None of the patients with decreased renal function had a history of any renal disease or anomaly, renal stones, or had nephrocalcinosis on their last ultrasound.

Of the eight patients who had received (n=5) or were listed (n=3) for intestinal transplantation after a median of 90 (7–170) PN months, five showed decreased GFR in the evaluations performed at listing. Of the five patients with decreased GFR, four had Hirschsprung disease and one had NEC with 16%, 21%, 25%, 25% and 23% of remaining small intestine, respectively, and the median duration of PN was 99 months (80-153). Among the five patients with decreased renal function, median GFR was 66 (49–67) mL/min/1.73m^2 measured using ^{51}Cr-EDTA measurement in four of these cases.

Discussion

In this study, we found that renal function was impaired in 20 out of a total of 70 (29%) patients with pediatric onset IF after a median follow-up time of 5.3 years. Prolonged duration of PN and a short proportion of remaining small bowel were found to be associated with the decreased kidney function, suggesting that the severity of IF plays an important role. To our best knowledge, there are only two previous studies available on renal function in children with IF and/or with prolonged PN. According to the report by Moukarzel et al. including 13 children on long-term PN, all patients had impaired renal function (GFR 65.5±11.9 mL/min/1.73m^2) at a mean age of 9.0 ± 4.9 years [9]. The authors also found that in children with long-term PN,

the duration of PN was inversely correlated with GFR, similarly to the study carried out by Buchman et al. [5,9]. Recently, Kosar et al. published a study where they evaluated kidneys of 54 children with IF using serum creatinine and urea and urine oxalate, creatinine and calcium as biochemical parameters and renal ultrasonography. According to their report, a large proportion of the patients had increased echogenicity/nephrocalcinosis on ultrasonography analysis. Increased echogenicity/nephrocalcinosis was associated with prolonged PN exposure [8]. The authors did not report decreased renal function in any of the patients, but they did not measure GFR or calculate eGFR. Studies among adult IF patients have provided evidence for decreased renal function and a relatively high frequency of chronic renal failure [4-7]. Buchman et al. found a progressive impairment of renal function during prolonged PN. The rate of decline in creatinine clearance was 3.5 ± 6.3% per year [5]. In another study, renal function was studied in 33 patients on long-term PN and in 22 patients after intestinal transplantation. Chronic renal failure was found in 21% of the PN-dependent patients and in 54% of the transplanted patients [7]. Significant deterioration of kidney function also occurs following intestinal transplantation in children [10]. These findings are reinforced by the present study showing impaired renal function in a significant proportion of children with IF even after weaning off PN and in 5 out of 8 patients at listing for intestinal transplantation.

The pathophysiology of chronic renal failure in IF patients remains unclear.[4] It is most likely of multifactorial origin. Possible dehydration episodes, nephrolithiasis, repeated septicemias and exposure to nephrotoxic antimicrobial medication may all gradually deteriorate kidney function. The deterioration could be partly due to more novel mechanisms such as chronic low-grade renal inflammation induced by bacterial products, which translocate through leaky intestinal epithelium in SBS. In a study carried out by Lauverjat et al., 21 out of 40 (53%) adults with IF had a significant reduction in renal function, with a hypovolemic component in over 70% of the cases [6]. In addition to dehydration, the presence of urologic or nephrologic diseases was also found to be a risk factor for chronic renal failure [6]. There is also some

evidence suggesting that episodes of bacteremia and fungemia during PN are associated with a decline in GFR [5]. In this study, the number of blood culture-positive episodes of bacteremia or fungemia was not found to be associated with decreased renal function. The risk of calcium oxalate stones and/or nephrocalcinosis has also been found to be increased in patients with SBS and retained colon, which may lead to impairment of renal function [18]. The role of PN in the genesis of renal stones has been attributed to the acidity of solution and to the presence of vitamin C in PN, which leads to formation of urine oxalate formation [19]. Low calcium intake, vitamin D and hyperparathyreosis and the presence of lipid in the PN preparations can also have on impact on oxalate levels [20]. In this study, none of our patients with decreased renal function had nephrocalcinosis on ultrasonography or a history of kidney stones. Here, decreased renal function was equally prevalent during PN-dependency and after weaning off PN, highlighting the importance of close and continuing surveillance of kidney function in children with IF also after weaning off PN. The role of the amount of protein in the PN has also been studied in one earlier study, but no association between renal function and protein load was found [6].

In this study, patients with decreased renal function were shorter than patients with normal eGFR, suggesting that the growth of these patients has also been impacted by either the severity of IF or renal impairment. However, most of the patients with decreased renal function were not uremic, indicating a non-renal etiology in most cases.

Our patient material is one of the largest describing renal function in patients with IF. The study has, however, some limitations/weaknesses. As in the earlier study by Pironi et al. [7], we mainly used eGFR to evaluate renal function because measured GFR was not available from majority of the patients. In the recent study by Kosar et al. [8], creatinine alone was used to measure the glomerular function. In patients with IF, growth and muscle mass may be decreased, rendering creatinine alone an unreliable parameter of renal function, as was also

shown in this study. Here, we measured plasma cystatin C and urea concentrations almost exclusively and used the CKiD formula, which has been shown to correlate better with mGFR than formulas based only on creatinine or cystatin C concentration [14,21,22]. In the future, further studies measuring actual GFR in these patients are needed. Another caveat is that accurate information about the use of nephrotoxic medication was not available and we were thus unable to analyze possible associations between medication and renal function. Our hospital is a tertiary hospital and many of the study patients were managed at their local hospital between the follow-up visits. The possible impact of nephrotoxic medication has been evaluated in three earlier studies, suggesting that the medication does not have major impact on renal function [5,8,9].

Conclusions

In conclusion, patients with pediatric onset IF are at significant risk of impaired renal function, which, associated with the severity of SBS, may promote the development of chronic renal failure after intestinal transplantation. Therefore, evaluation of renal function of these patients is warranted.

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